



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :  
Jacques JOLIVET et al. : Examiner: Cybille Delacroix-Muirheid  
Serial No.: 10/806,336 : Group Art Unit: 1614  
Filed: March 23, 2004 :  
For: METHOD FOR ADMINISTRATION OF TROXACITABNE

**DECLARATION BY HENRIETTE GOURDEAU UNDER 37 CFR §1.132**  
**REGARDING PUBLICATIONS BY NON-INVENTOR AUTHORS**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

SIR:

I, Henriette Gourdeau, being duly warned, declare that:

I and Jacques Jolivet are the co-inventors of the claimed invention in the above-captioned application (see the attached list of claims).

I have been an employee of Shire BioChem Inc. since January 1995.

The instant application is assigned to Shire BioChem Inc.

I am a coauthor of the following publication: "Antitumor efficacy of troxacicabine given by continuous administration: The human HT-29 colon xenograft used as a tumor model," Proceedings of the American Association for Cancer Research, (1<sup>st</sup> Edition) Volume 44, Published March 2003, Abstract #2633.

The other authors listed on this publication are: Lorraine Leblond, Kelly Dong, Irenej Kianicka, Lucie Bibeau, Chantal Boudreau, Dominique Custeau, Lilianne Geerts, Annie Richard, Bettina Hamelin and Jacques Jolivet.

This publication relates to an in vivo study using mice, in which the feasibility of continuous infusion of troxacicabine was evaluated, which was performed for and under the direction, supervision and control of Shire BioChem Inc., and particularly under the direction, supervision and control of myself.

To the extent the claimed invention is disclosed in the above publication, coauthored by myself, Lorraine Leblond, Kelly Dong, Irenej Kianicka, Lucie Bibeau, Chantal Boudreau, Dominique Custeau, Lilianne Geerts, Annie Richard, Bettina Hamelin and Jacques Jolivet,

such disclosure is of mine and Jacques Jolivet's invention. The authors Lorraine Leblond, Kelly Dong, Irenej Kianicka, Lucie Bibeau, Chantal Boudreau, Dominique Custeau, Lilianne Geerts, and Annie Richard and Bettina Hamelin listed on the publication are not inventors, and contributed to aspects which were not part of the conception of the subject matter of the claims of this application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Henriette Gourdeau  
Henriette Gourdeau

Date: 10 Nov 2005

**List of Claims:**

1. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours wherein a steady state plasma concentration of troxacitabine of 0.03 to 2.0  $\mu$ M is achieved during the administration.
2. A method according to claim 1, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, pancreatic cancer, renal cancer, hepatoma, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphomas.
3. A method according to claim 2, wherein said cancer is pancreatic cancer.
4. A method according to claim 1, wherein said cancer is acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, or refractory myelodysplastic syndromes.
5. A method according to claim 4, wherein said cancer is acute myelogenous leukemia.
6. A method according to claim 2, wherein a steady state plasma concentration of 0.05 to 0.1  $\mu$ M is achieved during the administration.
7. A method according to claim 4, wherein a steady state plasma concentration of 0.1 to 0.42  $\mu$ M is achieved during the administration.
8. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein the maximum plasma concentration achieved during the administration is 0.03 to 2.0  $\mu$ M.
9. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 1.0  $\mu$ M..
10. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.5  $\mu$ M.
11. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.42  $\mu$ M.

12. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.1  $\mu$ M.

13. A method for the treatment of cancer within a patient, comprising administering to said patient troxacicabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours at a dose of 0.72 to 12.5 mg/m<sup>2</sup>/day.

14. A method according to claim 13, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 1.0 to 11.0 mg/m<sup>2</sup>/day.

15. A method according to claim 13, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 8.0 to 11.0 mg/m<sup>2</sup>/day.

16. A method according to claim 13, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, renal cancer, hepatoma, pancreatic cancer, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphoma.

17. A method according to claim 16, wherein said cancer is pancreatic cancer.

18. A method according to claim 13, wherein said cancer is acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, or refractory myelodysplastic syndromes.

19. A method according to claim 18, wherein said cancer is acute myelogenous leukemia.

20. A method according to claim 16, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 2.0 to 3.0 mg/m<sup>2</sup>/day.

21. A method according to claim 13, wherein said cancer is a solid tumor and the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day.

22. A method according to claim 18, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof 9.5 to 10.5mg/m<sup>2</sup>/day.

23. A method according to claim 1, wherein said continuous infusion is administered for a period of 3 to 7 days.

24. A method according to claim 1, wherein said continuous infusion is administered for a period of 3 days.

25. A method according to claim 1, wherein said continuous infusion is administered for a period of 4 days.

26. A method according to claim 1, wherein said continuous infusion is administered for a period of 5 days.

27. A method according to claim 1, wherein said continuous infusion is administered for a period of 6 days.

28. A method according to claim 1, wherein said continuous infusion is administered for a period of 7 days.

29. A method according to claim 16, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day, said period is 3 days, and a steady state plasma concentration of 0.05 to 0.1 μM of troxacicabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

30. A method according to claim 16, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day, said period is 4 days, and a steady state plasma concentration of 0.05 to 0.1 μM of troxacicabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

31. A method according to claim 18, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m<sup>2</sup>/day, said period is 5 days, and a steady state plasma concentration of 0.1 to 0.42 μM of troxacicabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

32. A method according to claim 18, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m<sup>2</sup>/day, said period is 6 days, and a steady state plasma concentration of 0.1 to 0.42 μM of troxacicabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

33. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 4 weeks.

34. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 3 weeks.

35. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 5 weeks.

36. A method according to claim 1 any one of the preceding claims, wherein said continuous infusion is by means of continuous intravenous infusion.

37. A method according to claim 1 any one of the preceding claims, wherein said method further comprising, in combination with said continuous administration of troxacitabine, administering at least one further therapeutic agent selected from the group comprising nucleoside analogues; chemotherapeutic agents; multidrug resistance reversing agents; and biological response modifiers.

38. A method according to claim 37, wherein said at least one further therapeutic agent is a chemotherapeutic agent selected from Asparaginase, Bleomycin, Busulfan, Carmustine, Chlorambucil, Cladribine, Cyclophosphamide, Cytarabine, Dacarbazine, Daunorubicin, Doxorubicin, Etoposide, Fludarabine, Gemcitabine, Gleevec®, Hydroxyurea, Idarubicin, Ifosfamide, Lomustine, Mechlorethamine, Melphalan, Mercaptourine, Methotrexate, Mitomycin, Mitoxantrone, Pentostatin, Procarbazine, 6-Thioguanine, Topotecan, Vinblastine, Vincristine, Dexamethasone, Retinoic acid and Prednisone.

39. A method according to claim 37, wherein said at least one further therapeutic agent is the multidrug resistance reversing agent PSC 833.

40. A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from monoclonal antibodies and cytokines.

41. A method according to claim 37, wherein said at least one further therapeutic agent is a cytokine selected from interferons, interleukins and colony-stimulating factors.

42. A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from Rituxan, CMA-676, Interferon-alpha recombinant, Interleukin-2, Interleukin-3, Erythropoietin, Epoetin, G-CSF, GM-CSF, Filgrastim, Sargramostim and Thrombopoietin.

43. A method according to claim 37 wherein said of troxacitabine or a pharmaceutically acceptable salt thereof and said at least one further therapeutic agent are administered sequentially.

44. A method according to claim 37 wherein said of troxacitabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered simultaneously.

45. A method according to claim 44 wherein said of troxacitabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in separate pharmaceutical formulations.

46. A method according to claim 44 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in combined pharmaceutical formulations.

47. A method for the administration of troxacicabine or a pharmaceutically acceptable salt thereof in a host having a tumor, comprising administering an amount of troxacicabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein said amount is sufficient to provide tumor reduction.



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In re application of :

Jacques JOLIVET et al. : Examiner: Cybille Delacroix-Muirheid

Serial No.: 10/806,336 : Group Art Unit: 1614

Filed: March 23, 2004 :

For: **METHOD FOR ADMINISTRATION OF TROXACITABNE**

**DECLARATION BY JACQUES JOVILET UNDER 37 CFR §1.132**  
**REGARDING PUBLICATIONS BY NON-INVENTOR AUTHORS**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

SIR:

I, Jacques Jolivet, being duly warned, declare that:

I and Henriette Gourdeau are the co-inventors of the claimed invention in the above-captioned application (see the attached list of claims).

I have been an employee of Shire BioChem Inc. since october 1998

The instant application is assigned to Shire BioChem Inc.

I am a coauthor of the following publication: "Antitumor efficacy of troxacicabine given by continuous administration: The human HT-29 colon xenograft used as a tumor model," Proceedings of the American Association for Cancer Research, (1<sup>st</sup> Edition) Volume 44, Published March 2003, Abstract #2633.

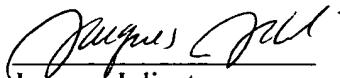
The other authors listed on this publication are: Lorraine Leblond, Kelly Dong, Irenej Kianicka, Lucie Bibeau, Chantal Boudreau, Dominique Custea, Lilianne Geerts, Annie Richard, Bettina Hamelin and Henriette Gourdeau.

This publication relates to an in vivo study using mice, in which the feasibility of continuous infusion of troxacicabine was evaluated, which was performed for and under the direction, supervision and control of Shire BioChem Inc., and particularly under the direction, supervision and control of Ms. Henriette Gourdeau.

To the extent the claimed invention is disclosed in the above publication, coauthored by myself, Lorraine Leblond, Kelly Dong, Irenej Kianicka, Lucie Bibeau, Chantal Boudreau, Dominique Custea, Lilianne Geerts, Annie Richard, Bettina Hamelin and Henriette

Gourdeau, such disclosure is of mine and Henriette Gourdeau 's invention. The authors Lorraine Leblond, Kelly Dong, Irenej Kianicka, Lucie Bibeau, Chantal Boudreau, Dominique Custea, Lilianne Geerts, Annie Richard and Bettina Hamelin listed on the publication are not inventors, and contributed to aspects which were not part of the conception of the subject matter of the claims of this application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

  
Jacques Jolivet

Date: 10 Nov 2005

**List of Claims:**

1. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours wherein a steady state plasma concentration of troxacitabine of 0.03 to 2.0  $\mu\text{M}$  is achieved during the administration.
2. A method according to claim 1, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, pancreatic cancer, renal cancer, hepatoma, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphomas.
3. A method according to claim 2, wherein said cancer is pancreatic cancer.
4. A method according to claim 1, wherein said cancer is acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, or refractory myelodysplastic syndromes.
5. A method according to claim 4, wherein said cancer is acute myelogenous leukemia.
6. A method according to claim 2, wherein a steady state plasma concentration of 0.05 to 0.1  $\mu\text{M}$  is achieved during the administration.
7. A method according to claim 4, wherein a steady state plasma concentration of 0.1 to 0.42  $\mu\text{M}$  is achieved during the administration.
8. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein the maximum plasma concentration achieved during the administration is 0.03 to 2.0  $\mu\text{M}$ .
9. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 1.0  $\mu\text{M}$ .
10. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.5  $\mu\text{M}$ .
11. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.42  $\mu\text{M}$ .

12. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.1  $\mu$ M.

13. A method for the treatment of cancer within a patient, comprising administering to said patient troxacicabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours at a dose of 0.72 to 12.5 mg/m<sup>2</sup>/day.

14. A method according to claim 13, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 1.0 to 11.0 mg/m<sup>2</sup>/day.

15. A method according to claim 13, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 8.0 to 11.0 mg/m<sup>2</sup>/day.

16. A method according to claim 13, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, renal cancer, hepatoma, pancreatic cancer, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphoma.

17. A method according to claim 16, wherein said cancer is pancreatic cancer.

18. A method according to claim 13, wherein said cancer is acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, or refractory myelodysplastic syndromes.

19. A method according to claim 18, wherein said cancer is acute myelogenous leukemia.

20. A method according to claim 16, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 2.0 to 3.0 mg/m<sup>2</sup>/day.

21. A method according to claim 13, wherein said cancer is a solid tumor and the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day.

22. A method according to claim 18, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof 9.5 to 10.5mg/m<sup>2</sup>/day.

23. A method according to claim 1, wherein said continuous infusion is administered for a period of 3 to 7 days.

24. A method according to claim 1, wherein said continuous infusion is administered for a period of 3 days.

25. A method according to claim 1, wherein said continuous infusion is administered for a period of 4 days.
26. A method according to claim 1, wherein said continuous infusion is administered for a period of 5 days.
27. A method according to claim 1, wherein said continuous infusion is administered for a period of 6 days.
28. A method according to claim 1, wherein said continuous infusion is administered for a period of 7 days.
29. A method according to claim 16, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day, said period is 3 days, and a steady state plasma concentration of 0.05 to 0.1 μM of troxacicabine or a pharmaceutically acceptable salt thereof is achieved during the administration.
30. A method according to claim 16, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day, said period is 4 days, and a steady state plasma concentration of 0.05 to 0.1 μM of troxacicabine or a pharmaceutically acceptable salt thereof is achieved during the administration.
31. A method according to claim 18, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m<sup>2</sup>/day, said period is 5 days, and a steady state plasma concentration of 0.1 to 0.42 μM of troxacicabine or a pharmaceutically acceptable salt thereof is achieved during the administration.
32. A method according to claim 18, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m<sup>2</sup>/day, said period is 6 days, and a steady state plasma concentration of 0.1 to 0.42 μM of troxacicabine or a pharmaceutically acceptable salt thereof is achieved during the administration.
33. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 4 weeks.
34. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 3 weeks.
35. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 5 weeks.

36. A method according to claim 1 any one of the preceding claims, wherein said continuous infusion is by means of continuous intravenous infusion.

37. A method according to claim 1 any one of the preceding claims, wherein said method further comprising, in combination with said continuous administration of troxacicabine, administering at least one further therapeutic agent selected from the group comprising nucleoside analogues; chemotherapeutic agents; multidrug resistance reversing agents; and biological response modifiers.

38. A method according to claim 37, wherein said at least one further therapeutic agent is a chemotherapeutic agent selected from Asparaginase, Bleomycin, Busulfan, Carmustine, Chlorambucil, Cladribine, Cyclophosphamide, Cytarabine, Dacarbazine, Daunorubicin, Doxorubicin, Etoposide, Fludarabine, Gemcitabine, Gleevec®, Hydroxyurea, Idarubicin, Ifosfamide, Lomustine, Mechlorethamine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitoxantrone, Pentostatin, Procarbazine, 6-Thioguanine, Topotecan, Vinblastine, Vincristine, Dexamethasone, Retinoic acid and Prednisone.

39. A method according to claim 37, wherein said at least one further therapeutic agent is the multidrug resistance reversing agent PSC 833.

40. A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from monoclonal antibodies and cytokines.

41. A method according to claim 37, wherein said at least one further therapeutic agent is a cytokine selected from interferons, interleukins and colony-stimulating factors.

42. A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from Rituxan, CMA-676, Interferon-alpha recombinant, Interleukin-2, Interleukin-3, Erythropoetin, Epoetin, G-CSF, GM-CSF, Filgrastim, Sargramostim and Thrombopoietin.

43. A method according to claim 37 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and said at least one further therapeutic agent are administered sequentially.

44. A method according to claim 37 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered simultaneously.

45. A method according to claim 44 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in separate pharmaceutical formulations.

46. A method according to claim 44 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in combined pharmaceutical formulations.

47. A method for the administration of troxacicabine or a pharmaceutically acceptable salt thereof in a host having a tumor, comprising administering an amount of troxacicabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein said amount is sufficient to provide tumor reduction.



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Jacques JOLIVET et al. : Examiner: Cybille Delacroix-Muirheid

Serial No.: 10/806,336 : Group Art Unit: 1614

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For: METHOD FOR ADMINISTRATION OF TROXACITABNE

**DECLARATION UNDER 37 CFR §1.132 REGARDING PUBLICATIONS BY NON-INVENTOR AUTHORS**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

SIR:

I, Kelly Dong, being duly warned, declare that:

I have reviewed the attached set of claims from patent application Serial No. 10/806,336.

I am a coauthor of the following publication: "Antitumor efficacy of troxacicabine given by continuous administration: The human HT-29 colon xenograft used as a tumor model," Proceedings of the American Association for Cancer Research, (1<sup>st</sup> Edition) Volume 44, Published March 2003, Abstract #2633.

*mice (rat) 21 Aug 06*

This publication relates to an in vivo study using ~~rats~~, in which the feasibility of continuous infusion of troxacicabine was evaluated, which was performed for and under the direction, supervision and control of Shire BioChem Inc., and particularly under the direction, supervision and control of Ms. Bettina Hamelin.

My role in this study was to perform research, as described in the publication, pursuant to instructions from Shire BioChem. At that time I was an employee of Shire BioChem and performed this work as part of my employment for Shire BioChem. All of my activities associated with this study were under the control of Shire BioChem.

I am not an inventor of the subject matter described in the above-mentioned publication and/or described in the attached set of claims.

I hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.



Kelly Dong

Date: 26-Sept-2005

**List of Claims:**

1. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacicabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours wherein a steady state plasma concentration of troxacicabine of 0.03 to 2.0  $\mu\text{M}$  is achieved during the administration.
2. A method according to claim 1, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, pancreatic cancer, renal cancer, hepatoma, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphomas.
3. A method according to claim 2, wherein said cancer is pancreatic cancer.
4. A method according to claim 1, wherein said cancer is acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, or refractory myelodysplastic syndromes.
5. A method according to claim 4, wherein said cancer is acute myelogenous leukemia.
6. A method according to claim 2, wherein a steady state plasma concentration of 0.05 to 0.1  $\mu\text{M}$  is achieved during the administration.
7. A method according to claim 4, wherein a steady state plasma concentration of 0.1 to 0.42  $\mu\text{M}$  is achieved during the administration.
8. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacicabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein the maximum plasma concentration achieved during the administration is 0.03 to 2.0  $\mu\text{M}$ .
9. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 1.0  $\mu\text{M}$ .
10. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.5  $\mu\text{M}$ .
11. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.42  $\mu\text{M}$ .

12. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.1  $\mu$ M.

13. A method for the treatment of cancer within a patient, comprising administering to said patient troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours at a dose of 0.72 to 12.5 mg/m<sup>2</sup>/day.

14. A method according to claim 13, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 1.0 to 11.0 mg/m<sup>2</sup>/day.

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36. A method according to claim 1 any one of the preceding claims, wherein said continuous infusion is by means of continuous intravenous infusion.

37. A method according to claim 1 any one of the preceding claims, wherein said method further comprising, in combination with said continuous administration of troxacicabine, administering at least one further therapeutic agent selected from the group comprising nucleoside analogues; chemotherapeutic agents; multidrug resistance reversing agents; and biological response modifiers.

38. A method according to claim 37, wherein said at least one further therapeutic agent is a chemotherapeutic agent selected from Asparaginase, Bleomycin, Busulfan, Carmustine, Chlorambucil, Cladribine, Cyclophosphamide, Cytarabine, Dacarbazine, Daunorubicin, Doxorubicin, Etoposide, Fludarabine, Gemcitabine, Gleevec®, Hydroxyurea, Idarubicin, Ifosfamide, Lomustine, Mechlorethamine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitoxantrone, Pentostatin, Procarbazine, 6-Thioguanine, Topotecan, Vinblastine, Vincristine, Dexamethasone, Retinoic acid and Prednisone.

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43. A method according to claim 37 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and said at least one further therapeutic agent are administered sequentially.

44. A method according to claim 37 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered simultaneously.

45. A method according to claim 44 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in separate pharmaceutical formulations.

46. A method according to claim 44 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in combined pharmaceutical formulations.

47. A method for the administration of troxacicabine or a pharmaceutically acceptable salt thereof in a host having a tumor, comprising administering an amount of troxacicabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein said amount is sufficient to provide tumor reduction.



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

1. re application of :  
Jacques JOLIVET et al.

: Examiner: Cybille Delacroix-Muirheid

Serial No.: 10/806,336 : Group Art Unit: 1614

Filed: March 23, 2004 :  
For: METHOD FOR ADMINISTRATION OF TROXACITABINE

**DECLARATION UNDER 37 CFR §1.132 REGARDING PUBLICATIONS BY NON-INVENTOR AUTHORS**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

SIR:

I, Irenej Kianicka, being duly warned, declare that:

I have reviewed the attached set of claims from patent application Serial No. 10/806,336.

I am a coauthor of the following publication: "Antitumor efficacy of troxacitabine given by continuous administration: The human HT-29 colon xenograft used as a tumor model," Proceedings of the American Association for Cancer Research, (1<sup>st</sup> Edition) Volume 44, Published March 2003, Abstract #2633. *IK*

This publication relates to an in vivo study using *mice*, in which the feasibility of continuous infusion of troxacitabine was evaluated, which was performed for and under the direction, supervision and control of Shire BioChem Inc., and particularly under the direction, supervision and control of Ms. Henriette Gourdeau.

My role in this study was to perform research, as described in the publication, pursuant to instructions from Shire BioChem. At that time I was an employee of Shire BioChem and performed this work as part of my employment for Shire BioChem. All of my activities associated with this study were under the control of Shire BioChem.

I am not an inventor of the subject matter described in the above-mentioned publication and/or described in the attached set of claims.

I hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon. \*

Irenej Kianicka  
Irenej Kianicka  
Date: Oct. 20/2005

\*VR - I cannot confrom exactitude of the Claims on pages 3-7 due to the elapsed time since I was working in this project and due to not having access to the original data.

I.K.

I.K.

List of Claims:

1. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacicabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours wherein a steady state plasma concentration of troxacicabine of 0.03 to 2.0  $\mu$ M is achieved during the administration.
2. A method according to claim 1, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, pancreatic cancer, renal cancer, hepatoma, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphomas.
3. A method according to claim 2, wherein said cancer is pancreatic cancer.
4. A method according to claim 1, wherein said cancer is acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, or refractory myelodysplastic syndromes.
5. A method according to claim 4, wherein said cancer is acute myelogenous leukemia.
6. A method according to claim 2, wherein a steady state plasma concentration of 0.05 to 0.1  $\mu$ M is achieved during the administration.
7. A method according to claim 4, wherein a steady state plasma concentration of 0.1 to 0.42  $\mu$ M is achieved during the administration.
8. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacicabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein the maximum plasma concentration achieved during the administration is 0.03 to 2.0  $\mu$ M.
9. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 1.0  $\mu$ M.
10. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.5  $\mu$ M.
11. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.42  $\mu$ M.

12. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.1  $\mu$ M.

13. A method for the treatment of cancer within a patient, comprising administering to said patient troxacicabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours at a dose of 0.72 to 12.5 mg/m<sup>2</sup>/day.

14. A method according to claim 13, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 1.0 to 11.0 mg/m<sup>2</sup>/day.

15. A method according to claim 13, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 8.0 to 11.0 mg/m<sup>2</sup>/day.

16. A method according to claim 13, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, renal cancer, hepatoma, pancreatic cancer, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphoma.

17. A method according to claim 16, wherein said cancer is pancreatic cancer.

18. A method according to claim 13, wherein said cancer is acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, or refractory myelodysplastic syndromes.

19. A method according to claim 18, wherein said cancer is acute myelogenous leukemia.

20. A method according to claim 16, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 2.0 to 3.0 mg/m<sup>2</sup>/day.

21. A method according to claim 13, wherein said cancer is a solid tumor and the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day.

22. A method according to claim 18, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof 9.5 to 10.5mg/m<sup>2</sup>/day.

23. A method according to claim 1, wherein said continuous infusion is administered for a period of 3 to 7 days.

24. A method according to claim 1, wherein said continuous infusion is administered for a period of 3 days.

25. A method according to claim 1, wherein said continuous infusion is administered for a period of 4 days.

26. A method according to claim 1, wherein said continuous infusion is administered for a period of 5 days.

27. A method according to claim 1, wherein said continuous infusion is administered for a period of 6 days.

28. A method according to claim 1, wherein said continuous infusion is administered for a period of 7 days.

29. A method according to claim 16, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day, said period is 3 days, and a steady state plasma concentration of 0.05 to 0.1 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

30. A method according to claim 16, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day, said period is 4 days, and a steady state plasma concentration of 0.05 to 0.1 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

31. A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m<sup>2</sup>/day, said period is 5 days, and a steady state plasma concentration of 0.1 to 0.42 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

32. A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m<sup>2</sup>/day, said period is 6 days, and a steady state plasma concentration of 0.1 to 0.42 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

33. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 4 weeks.

34. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 3 weeks.

35. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 5 weeks.



36. A method according to claim 1 any one of the preceding claims, wherein said continuous infusion is by means of continuous intravenous infusion.

37. A method according to claim 1 any one of the preceding claims, wherein said method further comprising, in combination with said continuous administration of troxacicabine, administering at least one further therapeutic agent selected from the group comprising nucleoside analogues; chemotherapeutic agents; multidrug resistance reversing agents; and biological response modifiers.

38. A method according to claim 37, wherein said at least one further therapeutic agent is a chemotherapeutic agent selected from Asparaginase, Bleomycin, Busulfan, Carmustine, Chlorambucil, Cladribine, Cyclophosphamide, Cytarabine, Dacarbazine, Daunorubicin, Doxorubicin, Etoposide, Fludarabine, Gemcitabine, Gleevec®, Hydroxyurea, Idarubicin, Ifosfamide, Lomustine, Mechlorethamine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitoxantrone, Pentostatin, Procarbazine, 6-Thioguanine, Topotecan, Vinblastine, Vincristine, Dexamethasone, Retinoic acid and Prednisone.

39. A method according to claim 37, wherein said at least one further therapeutic agent is the multidrug resistance reversing agent PSC 833.

40. A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from monoclonal antibodies and cytokines.

41. A method according to claim 37, wherein said at least one further therapeutic agent is a cytokine selected from interferons, interleukins and colony-stimulating factors.

42. A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from Rituxan, CMA-676, Interferon-alpha recombinant, Interleukin-2, Interleukin-3, Erythropoietin, Epoetin, G-CSF, GM-CSF, Filgrastim, Sargramostim and Thrombopoietin.

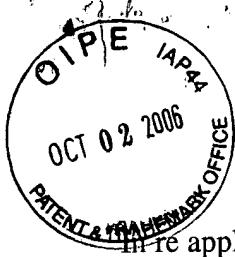
43. A method according to claim 37 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and said at least one further therapeutic agent are administered sequentially.

44. A method according to claim 37 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered simultaneously.

45. A method according to claim 44 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in separate pharmaceutical formulations.

46. A method according to claim 44 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in combined pharmaceutical formulations.

47. A method for the administration of troxacicabine or a pharmaceutically acceptable salt thereof in a host having a tumor, comprising administering an amount of troxacicabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein said amount is sufficient to provide tumor reduction.



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Jacques JOLIVET et al. : Examiner: Cybille Delacroix-Muirheid

Serial No.: 10/806,336 : Group Art Unit: 1614

Filed: March 23, 2004 :

For: METHOD FOR ADMINISTRATION OF TROXACITABNE

**DECLARATION UNDER 37 CFR §1.132 REGARDING PUBLICATIONS BY NON-INVENTOR AUTHORS**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

SIR:

I, Lucie Bibeau, being duly warned, declare that:

I have reviewed the attached set of claims from patent application Serial No. 10/806,336.

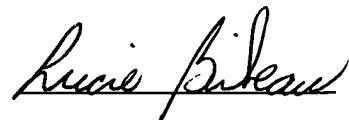
I am a coauthor of the following publication: "Antitumor efficacy of troxacicabine given by continuous administration: The human HT-29 colon xenograft used as a tumor model," Proceedings of the American Association for Cancer Research, (1<sup>st</sup> Edition) Volume 44, Published March 2003, Abstract #2633.

*24 week old mice AB*  
This publication relates to an in vivo study using ~~rats~~, in which the feasibility of continuous infusion of troxacicabine was evaluated, which was performed for and under the direction, supervision and control of Shire BioChem Inc., and particularly under the direction, supervision and control of Ms. Lorraine Leblond and Henriette Gourdeau.

My role in this study was to perform research, as described in the publication, pursuant to instructions from Shire BioChem. At that time I was an employee of Shire BioChem and performed this work as part of my employment for Shire BioChem. All of my activities associated with this study were under the control of Shire BioChem.

I am not an inventor of the subject matter described in the above-mentioned publication and/or described in the attached set of claims.

I hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

A handwritten signature in black ink, appearing to read "Lucie Bibeau".

Lucie Bibeau

Date: 23 Sept. 05

**List of Claims:**

1. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacicabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours wherein a steady state plasma concentration of troxacicabine of 0.03 to 2.0  $\mu\text{M}$  is achieved during the administration.
2. A method according to claim 1, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, pancreatic cancer, renal cancer, hepatoma, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphomas.
3. A method according to claim 2, wherein said cancer is pancreatic cancer.
4. A method according to claim 1, wherein said cancer is acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, or refractory myelodysplastic syndromes.
5. A method according to claim 4, wherein said cancer is acute myelogenous leukemia.
6. A method according to claim 2, wherein a steady state plasma concentration of 0.05 to 0.1  $\mu\text{M}$  is achieved during the administration.
7. A method according to claim 4, wherein a steady state plasma concentration of 0.1 to 0.42  $\mu\text{M}$  is achieved during the administration.
8. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacicabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein the maximum plasma concentration achieved during the administration is 0.03 to 2.0  $\mu\text{M}$ .
9. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 1.0  $\mu\text{M}$ .
10. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.5  $\mu\text{M}$ .
11. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.42  $\mu\text{M}$ .

12. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.1  $\mu$ M.

13. A method for the treatment of cancer within a patient, comprising administering to said patient troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours at a dose of 0.72 to 12.5 mg/m<sup>2</sup>/day.

14. A method according to claim 13, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 1.0 to 11.0 mg/m<sup>2</sup>/day.

15. A method according to claim 13, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 8.0 to 11.0 mg/m<sup>2</sup>/day.

16. A method according to claim 13, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, renal cancer, hepatoma, pancreatic cancer, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphoma.

17. A method according to claim 16, wherein said cancer is pancreatic cancer.

18. A method according to claim 13, wherein said cancer is acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, or refractory myelodysplastic syndromes.

19. A method according to claim 18, wherein said cancer is acute myelogenous leukemia.

20. A method according to claim 16, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 3.0 mg/m<sup>2</sup>/day.

21. A method according to claim 13, wherein said cancer is a solid tumor and the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day.

22. A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof 9.5 to 10.5mg/m<sup>2</sup>/day.

23. A method according to claim 1, wherein said continuous infusion is administered for a period of 3 to 7 days.

24. A method according to claim 1, wherein said continuous infusion is administered for a period of 3 days.

25. A method according to claim 1, wherein said continuous infusion is administered for a period of 4 days.
26. A method according to claim 1, wherein said continuous infusion is administered for a period of 5 days.
27. A method according to claim 1, wherein said continuous infusion is administered for a period of 6 days.
28. A method according to claim 1, wherein said continuous infusion is administered for a period of 7 days.
29. A method according to claim 16, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day, said period is 3 days, and a steady state plasma concentration of 0.05 to 0.1 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.
30. A method according to claim 16, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day, said period is 4 days, and a steady state plasma concentration of 0.05 to 0.1 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.
31. A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m<sup>2</sup>/day, said period is 5 days, and a steady state plasma concentration of 0.1 to 0.42 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.
32. A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m<sup>2</sup>/day, said period is 6 days, and a steady state plasma concentration of 0.1 to 0.42 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.
33. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 4 weeks.
34. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 3 weeks.
35. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 5 weeks.

36. A method according to claim 1 any one of the preceding claims, wherein said continuous infusion is by means of continuous intravenous infusion.

37. A method according to claim 1 any one of the preceding claims, wherein said method further comprising, in combination with said continuous administration of troxacicabine, administering at least one further therapeutic agent selected from the group comprising nucleoside analogues; chemotherapeutic agents; multidrug resistance reversing agents; and biological response modifiers.

38. A method according to claim 37, wherein said at least one further therapeutic agent is a chemotherapeutic agent selected from Asparaginase, Bleomycin, Busulfan, Carmustine, Chlorambucil, Cladribine, Cyclophosphamide, Cytarabine, Dacarbazine, Daunorubicin, Doxorubicin, Etoposide, Fludarabine, Gemcitabine, Gleevec®, Hydroxyurea, Idarubicin, Ifosfamide, Lomustine, Mechlorethamine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitoxantrone, Pentostatin, Procarbazine, 6-Thioguanine, Topotecan, Vinblastine, Vincristine, Dexamethasone, Retinoic acid and Prednisone.

39. A method according to claim 37, wherein said at least one further therapeutic agent is the multidrug resistance reversing agent PSC 833.

40. A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from monoclonal antibodies and cytokines.

41. A method according to claim 37, wherein said at least one further therapeutic agent is a cytokine selected from interferons, interleukins and colony-stimulating factors.

42. A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from Rituxan, CMA-676, Interferon-alpha recombinant, Interleukin-2, Interleukin-3, Erythropoetin, Epoetin, G-CSF, GM-CSF, Filgrastim, Sargramostim and Thrombopoietin.

43. A method according to claim 37 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and said at least one further therapeutic agent are administered sequentially.

44. A method according to claim 37 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered simultaneously.

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46. A method according to claim 44 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in combined pharmaceutical formulations.

47. A method for the administration of troxacicabine or a pharmaceutically acceptable salt thereof in a host having a tumor, comprising administering an amount of troxacicabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein said amount is sufficient to provide tumor reduction.



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Jacques JOLIVET et al. : Examiner: Cybille Delacroix-Muirheid

Serial No.: 10/806,336 : Group Art Unit: 1614

Filed: March 23, 2004 :

For: METHOD FOR ADMINISTRATION OF TROXACITABNE

**DECLARATION UNDER 37 CFR §1.132 REGARDING PUBLICATIONS BY NON-INVENTOR AUTHORS**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

SIR:

I, Chantal Boudreau, being duly warned, declare that:

I have reviewed the attached set of claims from patent application Serial No. 10/806,336.

I am a coauthor of the following publication: "Antitumor efficacy of troxacicabine given by continuous administration: The human HT-29 colon xenograft used as a tumor model," Proceedings of the American Association for Cancer Research, (1<sup>st</sup> Edition) Volume 44, Published March 2003, Abstract #2633.

This publication relates to an in vivo study using rats, in which the feasibility of continuous infusion of troxacicabine was evaluated, which was performed for and under the direction, supervision and control of Shire BioChem Inc., and particularly under the direction, supervision and control of Ms. Lorraine Leblond and Henriette Gourdeau.

My role in this study was to perform research, as described in the publication, pursuant to instructions from Shire BioChem. At that time I was an employee of Shire BioChem and performed this work as part of my employment for Shire BioChem. All of my activities associated with this study were under the control of Shire BioChem.

I am not an inventor of the subject matter described in the above-mentioned publication and/or described in the attached set of claims.

I hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Chantal Boudreau

Chantal Boudreau

Date: 23 sept. 2005

**List of Claims:**

1. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacicabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours wherein a steady state plasma concentration of troxacicabine of 0.03 to 2.0  $\mu\text{M}$  is achieved during the administration.
2. A method according to claim 1, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, pancreatic cancer, renal cancer, hepatoma, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphomas.
3. A method according to claim 2, wherein said cancer is pancreatic cancer.
4. A method according to claim 1, wherein said cancer is acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, or refractory myelodysplastic syndromes.
5. A method according to claim 4, wherein said cancer is acute myelogenous leukemia.
6. A method according to claim 2, wherein a steady state plasma concentration of 0.05 to 0.1  $\mu\text{M}$  is achieved during the administration.
7. A method according to claim 4, wherein a steady state plasma concentration of 0.1 to 0.42  $\mu\text{M}$  is achieved during the administration.
8. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacicabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein the maximum plasma concentration achieved during the administration is 0.03 to 2.0  $\mu\text{M}$ .
9. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 1.0  $\mu\text{M}$ .
10. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.5  $\mu\text{M}$ .
11. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.42  $\mu\text{M}$ .

12. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.1  $\mu$ M.
13. A method for the treatment of cancer within a patient, comprising administering to said patient troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours at a dose of 0.72 to 12.5 mg/m<sup>2</sup>/day.
14. A method according to claim 13, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 1.0 to 11.0 mg/m<sup>2</sup>/day.
15. A method according to claim 13, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 8.0 to 11.0 mg/m<sup>2</sup>/day.
16. A method according to claim 13, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, renal cancer, hepatoma, pancreatic cancer, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphoma.
17. A method according to claim 16, wherein said cancer is pancreatic cancer.
18. A method according to claim 13, wherein said cancer is acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, or refractory myelodysplastic syndromes.
19. A method according to claim 18, wherein said cancer is acute myelogenous leukemia.
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21. A method according to claim 13, wherein said cancer is a solid tumor and the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day.
22. A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof 9.5 to 10.5mg/m<sup>2</sup>/day.
23. A method according to claim 1, wherein said continuous infusion is administered for a period of 3 to 7 days.
24. A method according to claim 1, wherein said continuous infusion is administered for a period of 3 days.

25. A method according to claim 1, wherein said continuous infusion is administered for a period of 4 days.

26. A method according to claim 1, wherein said continuous infusion is administered for a period of 5 days.

27. A method according to claim 1, wherein said continuous infusion is administered for a period of 6 days.

28. A method according to claim 1, wherein said continuous infusion is administered for a period of 7 days.

29. A method according to claim 16, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day, said period is 3 days, and a steady state plasma concentration of 0.05 to 0.1 µM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

30. A method according to claim 16, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day, said period is 4 days, and a steady state plasma concentration of 0.05 to 0.1 µM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

31. A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m<sup>2</sup>/day, said period is 5 days, and a steady state plasma concentration of 0.1 to 0.42 µM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

32. A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m<sup>2</sup>/day, said period is 6 days, and a steady state plasma concentration of 0.1 to 0.42 µM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

33. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 4 weeks.

34. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 3 weeks.

35. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 5 weeks.

36. A method according to claim 1 any one of the preceding claims, wherein said continuous infusion is by means of continuous intravenous infusion.

37. A method according to claim 1 any one of the preceding claims, wherein said method further comprising, in combination with said continuous administration of troxacicabine, administering at least one further therapeutic agent selected from the group comprising nucleoside analogues; chemotherapeutic agents; multidrug resistance reversing agents; and biological response modifiers.

38. A method according to claim 37, wherein said at least one further therapeutic agent is a chemotherapeutic agent selected from Asparaginase, Bleomycin, Busulfan, Carmustine, Chlorambucil, Cladribine, Cyclophosphamide, Cytarabine, Dacarbazine, Daunorubicin, Doxorubicin, Etoposide, Fludarabine, Gemcitabine, Gleevec®, Hydroxyurea, Idarubicin, Ifosfamide, Lomustine, Mechlorethamine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitoxantrone, Pentostatin, Procarbazine, 6-Thioguanine, Topotecan, Vinblastine, Vincristine, Dexamethasone, Retinoic acid and Prednisone.

39. A method according to claim 37, wherein said at least one further therapeutic agent is the multidrug resistance reversing agent PSC 833.

40. A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from monoclonal antibodies and cytokines.

41. A method according to claim 37, wherein said at least one further therapeutic agent is a cytokine selected from interferons, interleukins and colony-stimulating factors.

42. A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from Rituxan, CMA-676, Interferon-alpha recombinant, Interleukin-2, Interleukin-3, Erythropoetin, Epoetin, G-CSF, GM-CSF, Filgrastim, Sargramostim and Thrombopoietin.

43. A method according to claim 37 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and said at least one further therapeutic agent are administered sequentially.

44. A method according to claim 37 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered simultaneously.

45. A method according to claim 44 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in separate pharmaceutical formulations.

46. A method according to claim 44 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in combined pharmaceutical formulations.

47. A method for the administration of troxacicabine or a pharmaceutically acceptable salt thereof in a host having a tumor, comprising administering an amount of troxacicabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein said amount is sufficient to provide tumor reduction.

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**



On re application of :

Jacques JOLIVET et al. : Examiner: Cybille Delacroix-Muirheid

Serial No.: 10/806,336 : Group Art Unit: 1614

Filed: March 23, 2004 :

For: METHOD FOR ADMINISTRATION OF TROXACITABNE

**DECLARATION UNDER 37 CFR §1.132 REGARDING PUBLICATIONS BY NON-INVENTOR AUTHORS**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

SIR:

I, Dominique Custea, being duly warned, declare that:

I have reviewed the attached set of claims from patent application Serial No. 10/806,336.

I am a coauthor of the following publication: "Antitumor efficacy of troxacicabine given by continuous administration: The human HT-29 colon xenograft used as a tumor model," Proceedings of the American Association for Cancer Research, (1<sup>st</sup> Edition) Volume 44, Published March 2003, Abstract #2633.

This publication relates to an in vivo study using mice, in which the feasibility of continuous infusion of troxacicabine was evaluated, which was performed for and under the direction, supervision and control of Shire BioChem Inc., and particularly under the direction, supervision and control of Ms. Lorraine Leblond and Henriette Gourdeau.

My role in this study was to perform research, as described in the publication, pursuant to instructions from Shire BioChem. At that time I was an employee of Shire BioChem and performed this work as part of my employment for Shire BioChem. All of my activities associated with this study were under the control of Shire BioChem.

I am not an inventor of the subject matter described in the above-mentioned publication and/or described in the attached set of claims.

I hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.



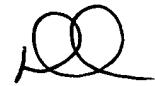
Dominique Custea

Date: Oct 13<sup>u</sup>, 2005

**List of Claims:**



1. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours wherein a steady state plasma concentration of troxacitabine of 0.03 to 2.0  $\mu$ M is achieved during the administration.
2. A method according to claim 1, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, pancreatic cancer, renal cancer, hepatoma, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphomas.
3. A method according to claim 2, wherein said cancer is pancreatic cancer.
4. A method according to claim 1, wherein said cancer is acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, or refractory myelodysplastic syndromes.
5. A method according to claim 4, wherein said cancer is acute myelogenous leukemia.
6. A method according to claim 2, wherein a steady state plasma concentration of 0.05 to 0.1  $\mu$ M is achieved during the administration.
7. A method according to claim 4, wherein a steady state plasma concentration of 0.1 to 0.42  $\mu$ M is achieved during the administration.
8. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein the maximum plasma concentration achieved during the administration is 0.03 to 2.0  $\mu$ M.
9. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 1.0  $\mu$ M.
10. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.5  $\mu$ M.
11. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.42  $\mu$ M.



12. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.1  $\mu$ M.

13. A method for the treatment of cancer within a patient, comprising administering to said patient troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours at a dose of 0.72 to 12.5 mg/m<sup>2</sup>/day.

14. A method according to claim 13, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 1.0 to 11.0 mg/m<sup>2</sup>/day.

15. A method according to claim 13, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 8.0 to 11.0 mg/m<sup>2</sup>/day.

16. A method according to claim 13, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, renal cancer, hepatoma, pancreatic cancer, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphoma.

17. A method according to claim 16, wherein said cancer is pancreatic cancer.

18. A method according to claim 13, wherein said cancer is acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, or refractory myelodysplastic syndromes.

19. A method according to claim 18, wherein said cancer is acute myelogenous leukemia.

20. A method according to claim 16, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 3.0 mg/m<sup>2</sup>/day.

21. A method according to claim 13, wherein said cancer is a solid tumor and the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day.

22. A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof 9.5 to 10.5mg/m<sup>2</sup>/day.

23. A method according to claim 1, wherein said continuous infusion is administered for a period of 3 to 7 days.

24. A method according to claim 1, wherein said continuous infusion is administered for a period of 3 days.



25. A method according to claim 1, wherein said continuous infusion is administered for a period of 4 days.
26. A method according to claim 1, wherein said continuous infusion is administered for a period of 5 days.
27. A method according to claim 1, wherein said continuous infusion is administered for a period of 6 days.
28. A method according to claim 1, wherein said continuous infusion is administered for a period of 7 days.
29. A method according to claim 16, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day, said period is 3 days, and a steady state plasma concentration of 0.05 to 0.1 μM of troxacicabine or a pharmaceutically acceptable salt thereof is achieved during the administration.
30. A method according to claim 16, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day, said period is 4 days, and a steady state plasma concentration of 0.05 to 0.1 μM of troxacicabine or a pharmaceutically acceptable salt thereof is achieved during the administration.
31. A method according to claim 18, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m<sup>2</sup>/day, said period is 5 days, and a steady state plasma concentration of 0.1 to 0.42 μM of troxacicabine or a pharmaceutically acceptable salt thereof is achieved during the administration.
32. A method according to claim 18, wherein the dosage amount of troxacicabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m<sup>2</sup>/day, said period is 6 days, and a steady state plasma concentration of 0.1 to 0.42 μM of troxacicabine or a pharmaceutically acceptable salt thereof is achieved during the administration.
33. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 4 weeks.
34. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 3 weeks.
35. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 5 weeks.

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36. A method according to claim 1 any one of the preceding claims, wherein said continuous infusion is by means of continuous intravenous infusion.

37. A method according to claim 1 any one of the preceding claims, wherein said method further comprising, in combination with said continuous administration of troxacitabine, administering at least one further therapeutic agent selected from the group comprising nucleoside analogues; chemotherapeutic agents; multidrug resistance reversing agents; and biological response modifiers.

38. A method according to claim 37, wherein said at least one further therapeutic agent is a chemotherapeutic agent selected from Asparaginase, Bleomycin, Busulfan, Carmustine, Chlorambucil, Cladribine, Cyclophosphamide, Cytarabine, Dacarbazine, Daunorubicin, Doxorubicin, Etoposide, Fludarabine, Gemcitabine, Gleevec®, Hydroxyurea, Idarubicin, Ifosfamide, Lomustine, Mechlorethamine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitoxantrone, Pentostatin, Procarbazine, 6-Thioguanine, Topotecan, Vinblastine, Vincristine, Dexamethasone, Retinoic acid and Prednisone.

39. A method according to claim 37, wherein said at least one further therapeutic agent is the multidrug resistance reversing agent PSC 833.

40. A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from monoclonal antibodies and cytokines.

41. A method according to claim 37, wherein said at least one further therapeutic agent is a cytokine selected from interferons, interleukins and colony-stimulating factors.

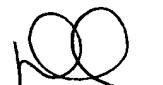
42. A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from Rituxan, CMA-676, Interferon-alpha recombinant, Interleukin-2, Interleukin-3, Erythropoetin, Epoetin, G-CSF, GM-CSF, Filgrastim, Sargramostim and Thrombopoietin.

43. A method according to claim 37 wherein said of troxacitabine or a pharmaceutically acceptable salt thereof and said at least one further therapeutic agent are administered sequentially.

44. A method according to claim 37 wherein said of troxacitabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered simultaneously.

45. A method according to claim 44 wherein said of troxacitabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in separate pharmaceutical formulations.

46. A method according to claim 44 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in combined pharmaceutical formulations.



47. A method for the administration of troxacicabine or a pharmaceutically acceptable salt thereof in a host having a tumor, comprising administering an amount of troxacicabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein said amount is sufficient to provide tumor reduction.



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Jacques JOLIVET et al. : Examiner: Cybille Delacroix-Muirheid

Serial No.: 10/806,336 : Group Art Unit: 1614

Filed: March 23, 2004 :

For: METHOD FOR ADMINISTRATION OF TROXACITABNE

**DECLARATION UNDER 37 CFR §1.132 REGARDING PUBLICATIONS BY NON-INVENTOR AUTHORS**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

SIR:

I, Annie Richard, being duly warned, declare that:

I have reviewed the attached set of claims from patent application Serial No. 10/806,336.

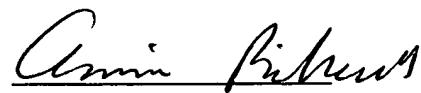
I am a coauthor of the following publication: "Antitumor efficacy of troxacicabine given by continuous administration: The human HT-29 colon xenograft used as a tumor model," Proceedings of the American Association for Cancer Research, (1<sup>st</sup> Edition) Volume 44, Published March 2003, Abstract #2633.

*mice AR 21-Aug-2006*  
This publication relates to an in vivo study using rats, in which the feasibility of continuous infusion of troxacicabine was evaluated, which was performed for and under the direction, supervision and control of Shire BioChem Inc., and particularly under the direction, supervision and control of Ms. Bettina Hamelin.

My role in this study was to perform research, as described in the publication, pursuant to instructions from Shire BioChem. At that time I was an employee of Shire BioChem and performed this work as part of my employment for Shire BioChem. All of my activities associated with this study were under the control of Shire BioChem.

I am not an inventor of the subject matter described in the above-mentioned publication and/or described in the attached set of claims.

I hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

A handwritten signature in black ink, appearing to read "Annie Richard".

Annie Richard

Date: 21-Sept-2005

**List of Claims:**

1. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacetabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours wherein a steady state plasma concentration of troxacetabine of 0.03 to 2.0  $\mu$ M is achieved during the administration.
2. A method according to claim 1, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, pancreatic cancer, renal cancer, hepatoma, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphomas.
3. A method according to claim 2, wherein said cancer is pancreatic cancer.
4. A method according to claim 1, wherein said cancer is acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, or refractory myelodysplastic syndromes.
5. A method according to claim 4, wherein said cancer is acute myelogenous leukemia.
6. A method according to claim 2, wherein a steady state plasma concentration of 0.05 to 0.1  $\mu$ M is achieved during the administration.
7. A method according to claim 4, wherein a steady state plasma concentration of 0.1 to 0.42  $\mu$ M is achieved during the administration.
8. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacetabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein the maximum plasma concentration achieved during the administration is 0.03 to 2.0  $\mu$ M.
9. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 1.0  $\mu$ M.
10. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.5  $\mu$ M.
11. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.42  $\mu$ M.

12. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.1  $\mu$ M.

13. A method for the treatment of cancer within a patient, comprising administering to said patient troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours at a dose of 0.72 to 12.5 mg/m<sup>2</sup>/day.

14. A method according to claim 13, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 1.0 to 11.0 mg/m<sup>2</sup>/day.

15. A method according to claim 13, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 8.0 to 11.0 mg/m<sup>2</sup>/day.

16. A method according to claim 13, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, renal cancer, hepatoma, pancreatic cancer, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphoma.

17. A method according to claim 16, wherein said cancer is pancreatic cancer.

18. A method according to claim 13, wherein said cancer is acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, or refractory myelodysplastic syndromes.

19. A method according to claim 18, wherein said cancer is acute myelogenous leukemia.

20. A method according to claim 16, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 3.0 mg/m<sup>2</sup>/day.

21. A method according to claim 13, wherein said cancer is a solid tumor and the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day.

22. A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof 9.5 to 10.5mg/m<sup>2</sup>/day.

23. A method according to claim 1, wherein said continuous infusion is administered for a period of 3 to 7 days.

24. A method according to claim 1, wherein said continuous infusion is administered for a period of 3 days.

25. A method according to claim 1, wherein said continuous infusion is administered for a period of 4 days.
26. A method according to claim 1, wherein said continuous infusion is administered for a period of 5 days.
27. A method according to claim 1, wherein said continuous infusion is administered for a period of 6 days.
28. A method according to claim 1, wherein said continuous infusion is administered for a period of 7 days.
29. A method according to claim 16, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day, said period is 3 days, and a steady state plasma concentration of 0.05 to 0.1 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.
30. A method according to claim 16, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day, said period is 4 days, and a steady state plasma concentration of 0.05 to 0.1 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.
31. A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m<sup>2</sup>/day, said period is 5 days, and a steady state plasma concentration of 0.1 to 0.42 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.
32. A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m<sup>2</sup>/day, said period is 6 days, and a steady state plasma concentration of 0.1 to 0.42 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.
33. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 4 weeks.
34. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 3 weeks.
35. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 5 weeks.

36. A method according to claim 1 any one of the preceding claims, wherein said continuous infusion is by means of continuous intravenous infusion.

37. A method according to claim 1 any one of the preceding claims, wherein said method further comprising, in combination with said continuous administration of troxacicabine, administering at least one further therapeutic agent selected from the group comprising nucleoside analogues; chemotherapeutic agents; multidrug resistance reversing agents; and biological response modifiers.

38. A method according to claim 37, wherein said at least one further therapeutic agent is a chemotherapeutic agent selected from Asparaginase, Bleomycin, Busulfan, Carmustine, Chlorambucil, Cladribine, Cyclophosphamide, Cytarabine, Dacarbazine, Daunorubicin, Doxorubicin, Etoposide, Fludarabine, Gemcitabine, Gleevec®, Hydroxyurea, Idarubicin, Ifosfamide, Lomustine, Mechlorethamine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitoxantrone, Pentostatin, Procarbazine, 6-Thioguanine, Topotecan, Vinblastine, Vincristine, Dexamethasone, Retinoic acid and Prednisone.

39. A method according to claim 37, wherein said at least one further therapeutic agent is the multidrug resistance reversing agent PSC 833.

40. A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from monoclonal antibodies and cytokines.

41. A method according to claim 37, wherein said at least one further therapeutic agent is a cytokine selected from interferons, interleukins and colony-stimulating factors.

42. A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from Rituxan, CMA-676, Interferon-alpha recombinant, Interleukin-2, Interleukin-3, Erythropoetin, Epoetin, G-CSF, GM-CSF, Filgrastim, Sargramostim and Thrombopoietin.

43. A method according to claim 37 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and said at least one further therapeutic agent are administered sequentially.

44. A method according to claim 37 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered simultaneously.

45. A method according to claim 44 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in separate pharmaceutical formulations.

46. A method according to claim 44 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in combined pharmaceutical formulations.

47. A method for the administration of troxacicabine or a pharmaceutically acceptable salt thereof in a host having a tumor, comprising administering an amount of troxacicabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein said amount is sufficient to provide tumor reduction.



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :  
Jacques JOLIVET et al. : Examiner: Cybille Delacroix-Muirheid  
Serial No.: 10/806,336 : Group Art Unit: 1614  
Filed: March 23, 2004 :  
For: METHOD FOR ADMINISTRATION OF TROXACITABNE

**DECLARATION UNDER 37 CFR §1.132 REGARDING PUBLICATIONS BY NON-INVENTOR AUTHORS**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

SIR:

I, Bettina Hamelin, being duly warned, declare that:

I have reviewed the attached set of claims from patent application Serial No. 10/806,336.

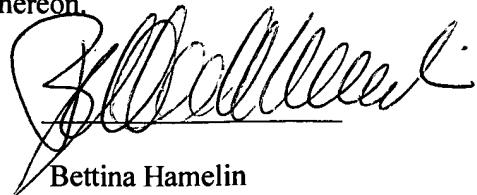
I am a coauthor of the following publication: "Antitumor efficacy of troxacitabine given by continuous administration: The human HT-29 colon xenograft used as a tumor model," Proceedings of the American Association for Cancer Research, (1<sup>st</sup> Edition) Volume 44, Published March 2003, Abstract #2633.

This publication relates to an in vivo study using mice, in which the feasibility of continuous infusion of troxacitabine was evaluated, which was performed for and under the direction, supervision and control of Shire BioChem Inc.

My role in this study was to perform research, as described in the publication, pursuant to instructions from Shire BioChem. At that time I was an employee of Shire BioChem and performed this work as part of my employment for Shire BioChem. All of my activities associated with this study were under the control of Shire BioChem.

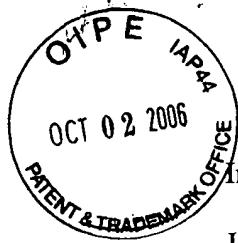
I am not an inventor of the subject matter described in the above-mentioned publication and/or described in the attached set of claims.

I hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.



Bettina Hamelin

Date: Sept 4, 06



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Jacques JOLIVET et al. : Examiner: Cybille Delacroix-Muirheid

Serial No.: 10/806,336 : Group Art Unit: 1614

Filed: March 23, 2004 :

For: METHOD FOR ADMINISTRATION OF TROXACITABNE

**DECLARATION UNDER 37 CFR §1.132 REGARDING PUBLICATIONS BY NON-INVENTOR AUTHORS**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

SIR:

I, Lorraine Leblond, being duly warned, declare that:

I have reviewed the attached set of claims from patent application Serial No. 10/806,336.

I am a coauthor of the following publication: "Antitumor efficacy of troxacicabine given by continuous administration: The human HT-29 colon xenograft used as a tumor model," Proceedings of the American Association for Cancer Research, (1<sup>st</sup> Edition) Volume 44, Published March 2003, Abstract #2633.

This publication relates to an in vivo study using mice, in which the feasibility of continuous infusion of troxacicabine was evaluated, which was performed for and under the direction, supervision and control of Shire BioChem Inc.

My role in this study was to perform research, as described in the publication, pursuant to instructions from Shire BioChem. At that time I was an employee of Shire BioChem and performed this work as part of my employment for Shire BioChem. All of my activities associated with this study were under the control of Shire BioChem.

I am not an inventor of the subject matter described in the above-mentioned publication and/or described in the attached set of claims.

I hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Lorraine Leblond

Lorraine Leblond

Date: 12 September 2006

**List of Claims:**

1. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours wherein a steady state plasma concentration of troxacitabine of 0.03 to 2.0  $\mu$ M is achieved during the administration.
2. A method according to claim 1, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, pancreatic cancer, renal cancer, hepatoma, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphomas.
3. A method according to claim 2, wherein said cancer is pancreatic cancer.
4. A method according to claim 1, wherein said cancer is acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, or refractory myelodysplastic syndromes.
5. A method according to claim 4, wherein said cancer is acute myelogenous leukemia.
6. A method according to claim 2, wherein a steady state plasma concentration of 0.05 to 0.1  $\mu$ M is achieved during the administration.
7. A method according to claim 4, wherein a steady state plasma concentration of 0.1 to 0.42  $\mu$ M is achieved during the administration.
8. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein the maximum plasma concentration achieved during the administration is 0.03 to 2.0  $\mu$ M.
9. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 1.0  $\mu$ M.
10. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.5  $\mu$ M.
11. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.42  $\mu$ M.

12. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.1  $\mu$ M.

13. A method for the treatment of cancer within a patient, comprising administering to said patient troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours at a dose of 0.72 to 12.5 mg/m<sup>2</sup>/day.

14. A method according to claim 13, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 1.0 to 11.0 mg/m<sup>2</sup>/day.

15. A method according to claim 13, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 8.0 to 11.0 mg/m<sup>2</sup>/day.

16. A method according to claim 13, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, renal cancer, hepatoma, pancreatic cancer, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphoma.

17. A method according to claim 16, wherein said cancer is pancreatic cancer.

18. A method according to claim 13, wherein said cancer is acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, or refractory myelodysplastic syndromes.

19. A method according to claim 18, wherein said cancer is acute myelogenous leukemia.

20. A method according to claim 16, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 3.0 mg/m<sup>2</sup>/day.

21. A method according to claim 13, wherein said cancer is a solid tumor and the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day.

22. A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof 9.5 to 10.5mg/m<sup>2</sup>/day.

23. A method according to claim 1, wherein said continuous infusion is administered for a period of 3 to 7 days.

24. A method according to claim 1, wherein said continuous infusion is administered for a period of 3 days.

25. A method according to claim 1, wherein said continuous infusion is administered for a period of 4 days.

26. A method according to claim 1, wherein said continuous infusion is administered for a period of 5 days.

27. A method according to claim 1, wherein said continuous infusion is administered for a period of 6 days.

28. A method according to claim 1, wherein said continuous infusion is administered for a period of 7 days.

29. A method according to claim 16, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day, said period is 3 days, and a steady state plasma concentration of 0.05 to 0.1 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

30. A method according to claim 16, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day, said period is 4 days, and a steady state plasma concentration of 0.05 to 0.1 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

31. A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m<sup>2</sup>/day, said period is 5 days, and a steady state plasma concentration of 0.1 to 0.42 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

32. A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m<sup>2</sup>/day, said period is 6 days, and a steady state plasma concentration of 0.1 to 0.42 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

33. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 4 weeks.

34. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 3 weeks.

35. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 5 weeks.

36. A method according to claim 1 any one of the preceding claims, wherein said continuous infusion is by means of continuous intravenous infusion.

37. A method according to claim 1 any one of the preceding claims, wherein said method further comprising, in combination with said continuous administration of troxacicabine, administering at least one further therapeutic agent selected from the group comprising nucleoside analogues; chemotherapeutic agents; multidrug resistance reversing agents; and biological response modifiers.

38. A method according to claim 37, wherein said at least one further therapeutic agent is a chemotherapeutic agent selected from Asparaginase, Bleomycin, Busulfan, Carmustine, Chlorambucil, Cladribine, Cyclophosphamide, Cytarabine, Dacarbazine, Daunorubicin, Doxorubicin, Etoposide, Fludarabine, Gemcitabine, Gleevec®, Hydroxyurea, Idarubicin, Ifosfamide, Lomustine, Mechlorethamine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitoxantrone, Pentostatin, Procarbazine, 6-Thioguanine, Topotecan, Vinblastine, Vincristine, Dexamethasone, Retinoic acid and Prednisone.

39. A method according to claim 37, wherein said at least one further therapeutic agent is the multidrug resistance reversing agent PSC 833.

40. A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from monoclonal antibodies and cytokines.

41. A method according to claim 37, wherein said at least one further therapeutic agent is a cytokine selected from interferons, interleukins and colony-stimulating factors.

42. A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from Rituxan, CMA-676, Interferon-alpha recombinant, Interleukin-2, Interleukin-3, Erythropoetin, Epoetin, G-CSF, GM-CSF, Filgrastim, Sargramostim and Thrombopoietin.

43. A method according to claim 37 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and said at least one further therapeutic agent are administered sequentially.

44. A method according to claim 37 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered simultaneously.

45. A method according to claim 44 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in separate pharmaceutical formulations.

46. A method according to claim 44 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in combined pharmaceutical formulations.

47. A method for the administration of troxacicabine or a pharmaceutically acceptable salt thereof in a host having a tumor, comprising administering an amount of troxacicabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein said amount is sufficient to provide tumor reduction.



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :  
Jacques JOLIVET et al. : Examiner: Cybille Delacroix-Muirheid  
Serial No.: 10/806,336 : Group Art Unit: 1614  
Filed: March 23, 2004 :  
For: METHOD FOR ADMINISTRATION OF TROXACITABNE

**DECLARATION UNDER 37 CFR §1.132 REGARDING PUBLICATIONS BY NON-INVENTOR AUTHORS**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

SIR:

I, Lilianne Geerts, being duly warned, declare that:

I have reviewed the attached set of claims from patent application Serial No. 10/806,336.

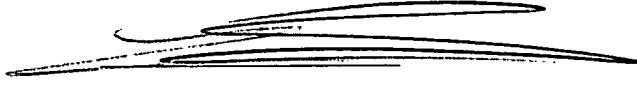
I am a coauthor of the following publication: "Antitumor efficacy of troxacitabine given by continuous administration: The human HT-29 colon xenograft used as a tumor model," Proceedings of the American Association for Cancer Research, (1<sup>st</sup> Edition) Volume 44, Published March 2003, Abstract #2633.

This publication relates to an in vivo study using mice, in which the feasibility of continuous infusion of troxacitabine was evaluated, which was performed for and under the direction, supervision and control of Shire BioChem Inc., and particularly under the direction, supervision and control of Ms. Lorraine Leblond and Henriette Gourdeau.

My role in this study was to perform research, as described in the publication, pursuant to instructions from Shire BioChem. At that time I was an employee of Shire BioChem and performed this work as part of my employment for Shire BioChem. All of my activities associated with this study were under the control of Shire BioChem.

I am not an inventor of the subject matter described in the above-mentioned publication and/or described in the attached set of claims.

I hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.



Lilianne Geerts

Date: 27 Oct 2005

*17e*

**List of Claims:**

1. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours wherein a steady state plasma concentration of troxacitabine of 0.03 to 2.0  $\mu\text{M}$  is achieved during the administration.
2. A method according to claim 1, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, pancreatic cancer, renal cancer, hepatoma, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphomas.
3. A method according to claim 2, wherein said cancer is pancreatic cancer.
4. A method according to claim 1, wherein said cancer is acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, or refractory myelodysplastic syndromes.
5. A method according to claim 4, wherein said cancer is acute myelogenous leukemia.
6. A method according to claim 2, wherein a steady state plasma concentration of 0.05 to 0.1  $\mu\text{M}$  is achieved during the administration.
7. A method according to claim 4, wherein a steady state plasma concentration of 0.1 to 0.42  $\mu\text{M}$  is achieved during the administration.
8. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein the maximum plasma concentration achieved during the administration is 0.03 to 2.0  $\mu\text{M}$ .
9. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 1.0  $\mu\text{M}$ .
10. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.5  $\mu\text{M}$ .
11. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.42  $\mu\text{M}$ .

12. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.1  $\mu$ M.

13. A method for the treatment of cancer within a patient, comprising administering to said patient troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours at a dose of 0.72 to 12.5 mg/m<sup>2</sup>/day.

14. A method according to claim 13, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 1.0 to 11.0 mg/m<sup>2</sup>/day.

15. A method according to claim 13, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 8.0 to 11.0 mg/m<sup>2</sup>/day.

16. A method according to claim 13, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, renal cancer, hepatoma, pancreatic cancer, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphoma.

17. A method according to claim 16, wherein said cancer is pancreatic cancer.

18. A method according to claim 13, wherein said cancer is acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, or refractory myelodysplastic syndromes.

19. A method according to claim 18, wherein said cancer is acute myelogenous leukemia.

20. A method according to claim 16, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 3.0 mg/m<sup>2</sup>/day.

21. A method according to claim 13, wherein said cancer is a solid tumor and the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day.

22. A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof 9.5 to 10.5mg/m<sup>2</sup>/day.

23. A method according to claim 1, wherein said continuous infusion is administered for a period of 3 to 7 days.

24. A method according to claim 1, wherein said continuous infusion is administered for a period of 3 days.

25. A method according to claim 1, wherein said continuous infusion is administered for a period of 4 days.

26. A method according to claim 1, wherein said continuous infusion is administered for a period of 5 days.

27. A method according to claim 1, wherein said continuous infusion is administered for a period of 6 days.

28. A method according to claim 1, wherein said continuous infusion is administered for a period of 7 days.

29. A method according to claim 16, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day, said period is 3 days, and a steady state plasma concentration of 0.05 to 0.1 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

30. A method according to claim 16, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day, said period is 4 days, and a steady state plasma concentration of 0.05 to 0.1 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

31. A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m<sup>2</sup>/day, said period is 5 days, and a steady state plasma concentration of 0.1 to 0.42 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

32. A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m<sup>2</sup>/day, said period is 6 days, and a steady state plasma concentration of 0.1 to 0.42 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

33. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 4 weeks.

34. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 3 weeks.

35. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 5 weeks.

36. A method according to claim 1 any one of the preceding claims, wherein said continuous infusion is by means of continuous intravenous infusion.

37. A method according to claim 1 any one of the preceding claims, wherein said method further comprising, in combination with said continuous administration of troxacitabine, administering at least one further therapeutic agent selected from the group comprising nucleoside analogues; chemotherapeutic agents; multidrug resistance reversing agents; and biological response modifiers.

38. A method according to claim 37, wherein said at least one further therapeutic agent is a chemotherapeutic agent selected from Asparaginase, Bleomycin, Busulfan, Carmustine, Chlorambucil, Cladribine, Cyclophosphamide, Cytarabine, Da carbazine, Daunorubicin, Doxorubicin, Etoposide, Fludarabine, Gemcitabine, Gleevec®, Hydroxyurea, Idarubicin, Ifosfamide, Lomustine, Mechlorethamine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitoxantrone, Pentostatin, Procarbazine, 6-Thioguanine, Topotecan, Vinblastine, Vincristine, Dexamethasone, Retinoic acid and Prednisone.

39. A method according to claim 37, wherein said at least one further therapeutic agent is the multidrug resistance reversing agent PSC 833.

40. A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from monoclonal antibodies and cytokines.

41. A method according to claim 37, wherein said at least one further therapeutic agent is a cytokine selected from interferons, interleukins and colony-stimulating factors.

42. A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from Rituxan, CMA-676, Interferon-alpha recombinant, Interleukin-2, Interleukin-3, Erythropoetin, Epoetin, G-CSF, GM-CSF, Filgrastim, Sargramostim and Thrombopoietin.

43. A method according to claim 37 wherein said of troxacitabine or a pharmaceutically acceptable salt thereof and said at least one further therapeutic agent are administered sequentially.

44. A method according to claim 37 wherein said of troxacitabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered simultaneously.

45. A method according to claim 44 wherein said of troxacitabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in separate pharmaceutical formulations.

46. A method according to claim 44 wherein said of troxacicabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in combined pharmaceutical formulations.

47. A method for the administration of troxacicabine or a pharmaceutically acceptable salt thereof in a host having a tumor, comprising administering an amount of troxacicabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein said amount is sufficient to provide tumor reduction.